

B6 18 (amended). The method according to Claim 17 wherein the total daily dosage is from about 1 gram to 10 grams day.

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### REMARKS

Claims 1 to 18 are in the application. Various claims have been amended to correct typographical errors or to better define the invention. The specification has been amended to correct an obvious grammatical error and to update the patent application information. No new matter is believed added.

A marked copy of the amendments to the claims and specification accompany this response as an appendix labeled "Marked Version to Show Changes Made".

### Rejection under 35 USC § 112

Claims 1 to 18 are rejected under 35 USC §112, second paragraph as being indefinite. Applicants respectfully traverse this rejection.

The Examiner has rejected claims 1 and 10 as being indefinite for the recitation of the term "cellulose derivative".

The Examiner states:

*"The scope of the term cellulose derivative is not fully described by the specification, and may read on a compound that comprises only a portion of a cellulose molecule".*

The term "cellulose derivative" is being read by the Examiner out of context with the rest of the claim language that precedes these two words, which are "water soluble, non-fermentable". These 3 words which are further exemplified in the specification on page 2, lines 17 to 20 as clearly indicating to the skilled artisan what is intended for use in practice of the invention disclosed herein. The water soluble non-fermentable cellulose derivatives are semi-synthetic fibers, which have been used for years as laxatives. The very references which the Examiner uses for the rejections under 35 USC §102 and §103 herein discuss the same fibers using the same or similar terminology.

Applicants have amended the spelling of psyllium in Claims 3 and 12 as noted by the Examiner.

Claims 6 and 15 have been amended to remove any lack of antecedent basis for the term cellulose as the claims from which they depend refer to "cellulose ether".

Claims 8, 9, 17 and 18 have also been amended to include the term "effective amount" to refer to the total daily dosage administered.

Claims 1 to 10 are also rejected under 35 USC §112, first paragraph as being non-enabling for the term "derivative". Applicants respectfully traverse this rejection.

The Examiner states that a :

*"disclosure of four species of cellulose derivatives is no adequate to describe the full scope of the cellulose derivatives as recited in claim 1 and 10".*

For the same reasons as those enunciated above for the §112, 2nd paragraph rejection, it is believed that the skilled artisan would readily understand what is contemplated by the term "water soluble, non-fermentable cellulose derivative" as you can not read one word out of context with the others preceding it within the same sentence. Dietary fiber is not a new art area. The type of fiber, which is indicated for use by these terms, is well known to the skilled artisan in this area. This term of art, for dietary fiber, is not the same as that of a "chemical compound". These fibers are generally higher molecular weight, natural or semi-synthetic fibers which have been modified and have their own art-recognized meanings.

Simply because Applicants have only listed four species under the grouping of "water soluble, non-fermentable cellulose derivatives" does not render the group indeterminate. These four species are the ones presently commercially available for sale in the US. A skilled artisan would know from reading this description what was intended for use as a dietary fiber component. It is not the number of species delineated which is important but that a suitably descriptive term, recognized by the group to which it is directed, along with exemplification of what is meant by that term that enables the skilled artisan to contemplate the proposed breadth of the invention.

Claims 1 to 3, 5 to 12, and 14 to 18 are also rejected under 35 USC §112, first paragraph as non enabling as to the combination of fibers other than with wheat bran. Applicants respectfully traverse this rejection.

It should be noted that the specification discloses naturally occurring soluble fibers (although fermentable) such as pectin, psyllium and guar gum on page 2, lines 29 and 30. While wheat bran is exemplified, the cited references (which are incorporated by reference) also include oat bran, and rice bran (see the Alabaster et al. article cited on page 2, lines 1 and 2 (copy enclosed).

The use of these dietary fibers as laxatives is well known, and well documented in the art. The total daily amounts, how they are administered, and in what form, etc. is well known. The present invention is directed to the use of particular fibers for a particular method, i.e. the reduction of the incidence of colon and breast cancer. The law does not require Applicants to provide a working example

in order to meet the requirements of enablement. However, Applicants do provide actual biological data in their specification.

The specification and the previously provided IDS/1449 also provide a "state of the art" stated by the Examiner to be missing. The specification further provides herein, both formulations, and daily dosages (page 6, lines 25 to 36 and page 7, lines 1 to 36) for practice of the invention. The specification, as noted above, also provides *in vivo* biological data in the form of a colon tumor model. This is an art recognized, suitable model for this field.

The Examiner comments that in view of the breadth of the claims, it would require undue experimentation to practice the claimed method to read on a combination of 2 soluble fibers without the addition of an insoluble fiber. This is not believed to be undue experimentation. However, the Examiner is reading the claims incorrectly in that the method requires the use of a water soluble, non-fermentable cellulose derivative alone or if desired in combination with an insoluble fiber, or a soluble fermentable fiber, or a combination of all three types of fibers. The invention teaches quite clearly how to determine each of these components, and provides a rational basis for such combination. The choice of fibers is also readily identifiable so that it is not seen how this falls under the guise of "undue experimentation".

In view of these remarks and amendments, reconsideration and withdrawal of the rejection to the claims under 35 USC §112, first and second paragraph is respectfully requested.

#### **Rejection under 35 USC § 102(e)**

Claims 1, 2, 5, 6, 8, and 9 are rejected under 35 USC §102 (e) as being anticipated by Annison et al., US patent 5,840,860. Applicants respectfully traverse this rejection.

Annison et al. is directed to a method of delivering short chain fatty acids (SCFA's), i.e. butyrates, to the lower bowl. This is meant to be a nutritional delivery of the SCFA's, a preferred fuel for the cells lining the lower bowel. Such a delivery may have use in diseases that effect the lower bowel, such as Inflammatory Bowel Disease.

A major difference between Annison et al. and the present invention is that the water soluble non-fermentable cellulose derivatives of the claims herein do not generate SCFA's. That is precisely the point of using a NON-FERMENTABLE fiber. See the specification on page 2, lines 29 to 31 that clearly describe other water soluble FERMENTABLE fibers as pectin, psyllium and guar gum. Hence, these fibers would

not meet the criteria of claim 1. In fact, the teachings of Annison et al. are directly opposing that of Applicants claimed invention.

Therefore, the teachings of Annison et al. do not anticipate Applicants claimed invention herein.

In light of these remarks and amendments, Applicants respectfully request reconsideration and withdrawal of the rejection to the claims under 35 USC §102 (e).

### **Rejection under 35 USC § 102(b)**

Claims 1, 2, 5, 6, 8, and 9 are rejected under 35 USC §102 (b) as being anticipated by Folino et al. (Folino, J. Nutr. 125: 1521-28, 1995). Applicants respectfully traverse this rejection.

Folio et al., teaches that epithelial proliferation, using a metaphase arrest method is dependent upon the type of fiber chosen for use, with methylcellulose > coarse wheat bran > fine wheat bran = rice bran > no fiber.

The end result of the Folino et al. article is epithelial proliferation. The epithelial proliferation looked for is that of the rapidly dividing tissues or cells in the colon. This marker or result is not the same as looking for cancerous, or neoplastic cell differentiation. The Folino et al. method does not measure tumors, or tumor growth in contrast to that described herein.

Folino et al. basically concludes that methylcellulose will increase the rate of cell division, have a high stool output, it is acidic and will not ferment, therefore no SCFA's will be present, and there will be no decrease in the pH. This result can be seen in the Abstract, wherein the effect on stool output is also described as ranking identically to that above. While this certainly confirms the use of methylcellulose as a laxative, it does not meet the preferred criteria of Folino et al. for the other desired aspects. The following sentence in the abstract discusses pH effects with most to least and methylcellulose is at the end, showing equal to a placebo or no fiber at all.

Folino et al. concludes that different fibers have different effects on the fecal environment, and are therefore hard to predict what the protective effect would be. This is the very point raised by the Examiner in the §112 rejection above. However, Applicants are not claiming a general grouping of all types of dietary fibers, but a grouping of non-fermentable water soluble cellulose fibers. Applicants in contrast to Folino also demonstrated positive data on reducing the incidence of tumors (the claimed end result).

Folino et al. teaches that you can feed fibers to rats. It does not teach that these fibers are protective against colon cancer, alone or with wheat bran. It does not demonstrate a benefit, just that different conditions and variables could generate or give rise to differing risks.

The present invention actually looks at a measure of colon carcinogenesis, a precursor to tumors. The two examples herein clearly demonstrates that use of a water soluble, non-fermentable cellulose ether, such as Methylcellulose is effective to reduce the risk of colon cancer, using the aberrant crypt foci (see Example 1) method. This method is an art - recognized method for measuring cancerous and precancerous conditions in contrast to what is described in the Folino et al. article.

Folino et al. does not measure cancer, or even a precancerous condition. Folino et al. does not teach a method from which one can reach Applicants conclusion, nor does Folino et al. show a reduction of tumors. From the Folino et al. article you find 1 positive (or pro feature) for methylcellulose and 3 negative (or con features) described therein.

Therefore, Folino et al. does not anticipate Applicants claimed invention.

In light of these remarks and amendments, Applicants respectfully request reconsideration and withdrawal of the rejection to the claims under 35 USC §102 (b).

### **Rejection under 35 USC §103**

Claims 10, 11, 14, 15 17 and 18 are rejected under 35 USC §103(a) as being unpatentable over Annison et al. , in view of Cohen et al. (J Nat'l Cancer Inst., 88(13): 899-907, 1996).

Claims 10, 11, 14, 15, 17, and 18 are rejected under 35 USC §103(a) as being unpatentable over Folino et al. in view of Cohen et al.

Claims 1, 4, 10 and 13 are rejected under 35 USC §103(a) as being unpatentable over Annison et al., or Folino et al, in view of Cohen et al. or Alabaster et al. (Cancer Letters 75: 53-58, 1993). Applicants respectfully traverse all of these rejections.

Applicants will address all of the §103 rejections together.

The present invention is directed to use of a water soluble, non-fermentable cellulose derivative, such as methylcellulose for the reduction of either colon cancer and/or breast cancer. It is not necessary to combine the methylcellulose with a second fiber, such as an insoluble fiber like wheat bran, or a soluble (but fermentable, fiber

like psyllium). The Examiner incorrectly interprets these claims to require such (page 8, first full paragraph of the office action).

Annison et al., as noted above, is directed to an entirely different invention, which is delivery of a nutritional SCFA to the lower bowel. The SCFA's, such as butyrate, are a fermentable by-product from the water soluble, fermentable fibers. There is no teachings, or motivation, in the Annison et al. patent taken alone or in combination with any of the other references to direct the skilled artisan to utilize a methylcellulose for the reduction of the incidence of colon or breast cancer.

The Examiner has previously been provided the cited references from the specification on page 2, lines 1 to 6. To summarize the history of this invention, subsequent to the Alabaster studies, it was shown that psyllium was not protective. The first Alabaster et al. reference (Alabaster I – Cancer Letters 75:53-58 , 1993) teach that wheat bran has a protective role, and that wheat bran in combination with psyllium is better than either alone. Alabaster II (Mutation Research 350:185-197, 1996), using the same type of experimental models, and the aberrant crypt foci method (as used herein), also concludes that wheat bran alone or in combination with psyllium and other nutrients, (see abstract) was effective to reduce aberrant crypt foci and colon tumors in their model.

Folino et al. shows that psyllium will decrease the pH, increase the level of butyrates (SCFA), increase output and as for proliferation, increase it over no fiber at all (placebo). Therefore, this article states that there are 3 positive measures for psyllium, and maybe one negative. Looking at this same article for methylcellulose, however, you are directed away from using methylcellulose over psyllium. Therefore, the skilled artisan would not be motivated to substitute an entirely different type of dietary fiber for psyllium.

Folino et al. also teaches, more importantly that the dietary fibers are not predictive, thereby teaching away from Applicants claimed invention. As previously noted, Folino et al. does not teach that the use of methylcellulose (or psyllium) would have a protective effect on carcinogenesis. Therefore, there is no motivation, taken alone or when combined with the other references which would direct the skilled artisan to the conclusion that methylcellulose would have a protective effect on colon cancer or breast cancer.

Cohen et al. is also a study on wheat bran and psyllium, but not water soluble non-fermentable cellulose derivatives. Similar to the Alabaster I and II studies, wheat bran is shown to be effective, and wheat bran in combination with psyllium is also effective to offer protection against breast cancer risk.

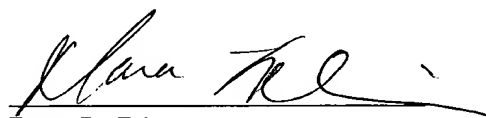
Cohen does not teach nor suggest the use of water soluble non-fermentable cellulose derivatives. None of these references provide a basis to substitute or to include with wheat bran or psyllium a methylcellulose like product and expect to achieve Applicants claimed invention herein.

In light of these remarks and amendments, Applicants respectfully request reconsideration and withdrawal of the rejection to the claims under 35 USC §103 (a).

### CONCLUSION

Should the Examiner have any questions or wish to discuss any aspect of this case, the Examiner is encouraged to call the undersigned at the number below. If any additional fees or charges are required by this paper the Commissioner is hereby authorized to charge Deposit account 19-2570 accordingly.

Respectfully submitted,



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MARKED VERSION TO SHOW CHANGES

In the Specification:

On page 3, lines 9 to 15 the following paragraph has been amended:

The present invention has found, unexpectedly that the combination of psyllium plus wheat bran was less [effect] effective than wheat bran alone or in combination with a water soluble cellulose derivative, such as methylcellulose. This combination of methylcellulose and wheat bran is more effective [that] than the widely accepted protective fiber, and better than the previously published combination therapy. Furthermore, the present invention, as shown below, also supports the proposition that enhanced protection is obtained by use of methylcellulose alone.

On page 7, lined 33 to 36 with the following paragraph has been amended:

A suitable, alternative formulation for use herein includes, but is not limited to the fast dissolving methylcellulose tablets as described in Daggy et al., WO 99/09958, [PCT/US98/17405,] filed 8/21/98, now US Patent 6,350,469 or WO 99/09959, [PCT/US98/17440,] filed 8/21/98, now USSN 09/485,625 (allowed) whose disclosures are incorporated herein by reference in their entirety.

In the Claims:

The following claims have been amended:

3 (2x amended). The method according to Claim 1, wherein the soluble fermentable fiber is [psyllium] psyllium.

6 (amended). The method according to Claim 2 wherein the cellulose ether is administered as bulk powder, a tablet, or suspension, which optionally contains sugar.

7 (amended). The method according to Claim 6 wherein the cellulose ether is administered in a rapidly disintegrating tablet.

8 (amended). The method according to Claim 1 wherein the effective amount is a total daily dosage [administered is] of from about 0.4 gram to 30 grams day.

9 (amended). The method according to Claim 8 wherein the total daily dosage [administered] is from about 1 gram to 10 grams day.



12 (2x amended). The method according to Claim 10, wherein the soluble fermentable fiber is [pysllium] psyllium.

15 (amended). The method according to Claim 11 wherein the cellulose ether is administered as bulk powder, a tablet, or suspension, which optionally contains sugar.

16 (amended). The method according to Claim 15 wherein the cellulose ether is administered in a rapidly disintegrating tablet.

17 (amended). The method according to Claim 10 wherein the effective amount is a total daily dosage [administered is] of from about 0.4 gram to 30 grams day.

18 (amended). The method according to Claim 17 wherein the total daily dosage [administered] is from about 1 gram to 10 grams day.